Complete Summary

GUIDELINE TITLE

Intravenous thrombolysis in acute myocardial infarctions. In: Sixth ACCP Consensus Conference on Antithrombotic Therapy.

BIBLIOGRAPHIC SOURCE(S)

Ohman EM, Harrington RA, Cannon CP, Agnelli G, Cairns JA, Kennedy JW. Intravenous thrombolysis in acute myocardial infarction. Chest 2001 Jan;119(1 Suppl):253S-277S. [188 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Acute myocardial infarction

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Cardiology
Critical Care
Emergency Medicine
Family Practice
Internal Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To provide an evidence-based set of recommendations for the use of fibrinolytic therapy in acute myocardial infarction
- To discuss the use of adjunctive antithrombotic therapies

TARGET POPULATION

Patients with acute myocardial infarction

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment

1. Intravenous fibrinolytic therapy
    a. Streptokinase
    b. Anistreplase
    c. Alteplase
    d. Reteplase
    e. Tenecteplase

    Note: Urokinase, single-chain urokinase-type plasminogen activator, lanoteplase, and staphylokinase were considered but not recommended.

2. Aspirin in combination with fibrinolytic therapy
3. Adjunctive therapy with thrombin inhibitors
    a. Heparin: unfractionated heparin
    b. Hirudin

    Note: Adjunctive therapy with other direct thrombin inhibitors, such as desirudin, lepirudin, and bivalirudin were considered but not recommended. In addition, adjunctive therapy with GP IIb/IIIa receptor blockers was considered but not recommended.

Evaluation of Therapeutic Efficacy

1. Angiographic assessment of epicardial coronary flow
2. Electrocardiogram evaluation

MAJOR OUTCOMES CONSIDERED

- Efficacy and safety of fibrinolytic therapy for acute myocardial infarction as defined by the following:
    - Rates of mortality
    - Rates of intracranial hemorrhage or other major bleeding
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The participants reviewed information from an exhaustive review of the literature.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The rating scheme framework captures the trade-off between benefits and risks (1 or 2) (see "Rating Scheme for the Strength of the Recommendations") and the methodologic quality of the underlying evidence (A, B, C+, or C).

Grades of evidence for antithrombotic agents:

1A
Methodological strength of supporting evidence: randomized controlled trials without important limitations

1B
Methodological strength of supporting evidence: randomized controlled trials with important limitations (inconsistent results, methodologic flaws*)

1C+
Methodological strength of supporting evidence: no randomized controlled trials, but randomized controlled trial results can be unequivocally extrapolated; or, overwhelming evidence from observational studies

1C
Methodological strength of supporting evidence: observation studies

2A
Methodological strength of supporting evidence: randomized controlled trials without important limitations

2B
Methodological strength of supporting evidence: randomized controlled trials with important limitations (inconsistent results, methodologic flaws*)

2C
Methodological strength of supporting evidence: observational studies

* Such situations include randomized controlled trials with lack of blinding, and subjective outcomes, in which the risk of bias in measurement of outcomes is high; and randomized controlled trials with large loss to follow-up.

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The strength of any recommendation depends on two factors: the trade-off between benefits and risks, and the strength of the methodology that leads to estimates of the treatment effect. The rating scheme used for this guideline captures these factors. The guideline developers grade the trade-off between benefits and risks in two categories: (1) the trade-off is clear enough that most patients, despite differences in values, would make the same choice; and (2) the trade-off is less clear, and each patient's values will likely lead to different choices.

When randomized trials provide precise estimates suggesting large treatment effects, and risks and costs of therapy are small, treatment for average patients with compatible values and preferences can be confidently recommended.

If the balance between benefits and risks is uncertain, methodologically rigorous studies providing grade A evidence and recommendations may still be weak (grade 2). Uncertainty may come from less precise estimates of benefit, harm, or costs, or from small effect sizes.

There is an independent impact of validity/consistency and the balance of positive and negative impacts of treatment on the strength of recommendations. In situations when there is doubt about the value of the trade-off, any recommendation will be weaker, moving from grade 1 to grade 2.

Grade 1 recommendations can only be made when there are precise estimates of both benefit and harm, and the balance between the two clearly favors recommending or not recommending the intervention for the average patient with compatible values and preferences. Table 2 of the original guideline document summarizes how a number of factors can reduce the strength of a recommendation, moving it from grade 1 to grade 2. Uncertainty about a recommendation to treat may be introduced if the target event that is trying to be prevented is less important (confident recommendations are more likely to be made to prevent death or stroke than asymptomatic deep venous thrombosis); if the magnitude of risk reduction in the overall group is small; if the risk is low in a particular subgroup of patients; if the estimate of the treatment effect, reflected in a wide confidence interval (CI) around the effect, is imprecise; if there is substantial potential harm associated with therapy; or if there is an expectation for a wide divergence in values even among average or typical patients. Higher costs would also lead to weaker recommendations to treat.

The more balanced the trade-off between benefits and risks, the greater the influence of individual patient values in decision making. If they understand the benefits and risks, virtually all patients will take aspirin after myocardial infarction or will comply with prophylaxis to reduce thromboembolism after hip replacement. Thus, one way of thinking about a grade 1 recommendation is that variability in patient values or individual physician values is unlikely to influence treatment choice in average or typical patients.

When the trade-off between benefits and risks is less clear, individual patient values will influence treatment decisions even among patients with average or typical preferences.

Grade 2 recommendations are those in which variation in patient values or individual physician values will often mandate different treatment choices, even among average or typical patients.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The rating scheme framework captures the trade-off between benefits and risks (1 or 2) and the methodologic quality of the underlying evidence (A, B, C+, or C) (see "Rating Scheme for the Strength of the Evidence").

Grades of recommendation for antithrombotic agents:

1A
Clarity of risk/benefit: risk/benefit clear
Implications: strong recommendation; can apply to most circumstances, without reservation

1B
Clarity of risk/benefit: risk/benefit clear
Implications: strong recommendation; likely to apply to most patients

1C+
Clarity of risk/benefit: risk/benefit clear

Implications: strong recommendation; can apply to most patients in most circumstances

1C
Clarity of risk/benefit: risk/benefit clear
Implications: intermediate-strength recommendation; may change when stronger evidence available

2A
Clarity of risk/benefit: risk/benefit unclear
Implications: intermediate strength recommendation; best action may differ, depending on circumstances or patients' societal values

2B
Clarity of risk/benefit: risk/benefit unclear
Implications: weak recommendation; alternative approaches likely to be better for some patients under some circumstances

2C
Clarity of risk/benefit: risk/benefit unclear
Implications: very weak recommendation; other alternatives may be equally reasonable

COST ANALYSIS

Cost-Effectiveness of Alteplase

A formal cost-effectiveness analysis was incorporated into the Global Utilization of Streptokinase and TPA (altepase) for Occluded Coronary Arteries (GUSTO-1) protocol as a substudy to be carried out in the United States and Canada. At 1 year, alteplase-treated patients had both higher costs ($2,845) and higher survival (an absolute 1.1% higher rate, or 11 more patients surviving per 1,000 patients treated) compared with streptokinase-treated patients. The incremental cost-effectiveness ratio was $32,678 per year of life saved. The use of alteplase in patients with anterior myocardial infarction (MI) yielded even more favorable cost-effectiveness values but less in inferior infarction and young patients. Thus, the cost-effectiveness of alteplase compared with streptokinase compares favorably with that of other therapies, such as hemodialysis for end-stage renal disease ($35,000 to $50,000 per year of life saved).

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The initial guidelines were prepared by the chapter committee (the primary authors) and then reviewed separately by the Committee Co-Chairs and methodology experts and finally by the entire group of Consensus Guideline participants.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

Excerpted by the National Guideline Clearinghouse (NGC):

The grading scheme is defined at the end of the Major Recommendations.

1. Fibrinolytic Therapy
    a. The guideline developers recommend that all patients with acute myocardial infarction who receive fibrinolytic therapy receive aspirin (165 to 325 milligrams) on arrival to the hospital and daily thereafter (grade 1A).
    b. The guideline developers recommend that patients with ischemic symptoms characteristic of acute myocardial infarction for 12 hours who have ST-segment elevation or left bundle-branch block on the electrocardiogram receive intravenous fibrinolytic therapy unless they have contraindications (grade 1A).
    c. For patients with symptoms characteristic of acute myocardial infarction and duration of 12 to 24 hours who have ST-segment elevation or left bundle-branch block on the electrocardiogram, the guideline developers recommend that intravenous fibrinolytic therapy should be considered (grade 2B).
    d. The guideline developers recommend that in patients with prior intracranial hemorrhage, any stroke within the past year, or active bleeding, clinicians do not administer intravenous fibrinolytic therapy (grade 1B).
    e. The guideline developers recommend that all patients with acute myocardial infarction who are candidates for fibrinolytic therapy receive it within 30 minutes after arrival to the hospital (grade 1A).

        For patients with symptom duration 12 hours, the guideline developers recommend administration of one of the fibrinolytic agents: streptokinase, anistreplase, or alteplase (all grade 1A in comparison to placebo).

        Remark: reteplase is equivalent to streptokinase.

    f. For patients with symptom duration 6 hours, the guideline developers recommend the administration of alteplase over streptokinase (grade 1A).

        Remark: tenecteplase is equivalent to alteplase.

    g. The guideline developers recommend that patients with known allergy or sensitivity to streptokinase receive alteplase, tenecteplase, or reteplase (grade 1C+).

2. Adjunctive Treatment With Thrombin Inhibitors
    a. Heparin
        1. For patients receiving streptokinase, the guideline developers recommend administration of subcutaneous unfractionated heparin (12,500 units every 12 hours for 48 hours) (grade 2A).
        2. For patients given streptokinase or anistreplase, the guideline developers recommend administration of intravenous unfractionated heparin only if they are at high risk of systemic or venous thromboembolism (anterior myocardial infarction, existing heart failure, previous embolus, atrial fibrillation, or left ventricular thrombus) (grade 1C).

           Remark: Heparin should be given not earlier than 4 hours after therapy and when the activated partial thromboplastin time is <70 seconds. The target activated partial thromboplastin time should be 50 to 70 s, and the infusion should continue for 48 h.

        3. For patients receiving alteplase (grade 1B*), reteplase (grade 1C*), or tenecteplase (grade 1C*), the guideline developers recommend administration of intravenous unfractionated heparin for 48 hours.
        4. For patients receiving intravenous heparin with alteplase, reteplase, or tenecteplase, the guideline developers recommend administration of either standard-dose unfractionated heparin (5,000-units bolus followed by 1,000 units per hour) (grade 1C*) or weight-adjusted dosing (60-units per kilogram bolus [4,000 units maximum] followed by 12 units per kilogram per hour [1,000 units per hour maximum]) (grade 2C), both adjusted to maintain an activated partial thromboplastin time of 50 to 70 s.

           *Note: The level of evidence ratings for items number 3 and 4 come from the Sixth ACCP Consensus Conference on Antithrombotic Therapy (2001): Summary recommendations. Northbrook, IL: ACCP, 2001. (Quick reference guide for clinicians).

    b. Direct Thrombin Inhibitors
        1. For patients with known or suspected heparin-induced thrombocytopenia or thrombosis who are receiving fibrinolytic therapy (either alteplase or streptokinase), the guideline developers recommend administration of intravenous hirudin (lepuridin 0.1-mg/kg bolus followed 0.15-mg/kg/hour infusion) (grade 2A).

The rating scheme framework captures the trade-off between benefits and risks (1 or 2) and the methodologic quality of the underlying evidence (A, B, C+, or C).

Definitions:

Grades of recommendations:

1A

Clarity of risk/benefit: risk/benefit clear
Methodological strength of supporting evidence: randomized controlled trials without important limitations
Implications: strong recommendation; can apply to most circumstances, without reservation

1B

Clarity of risk/benefit: risk/benefit clear
Methodological strength of supporting evidence: randomized controlled trials with important limitations (inconsistent results, methodologic flaws*)
Implications: strong recommendation; likely to apply to most patients

1C+

Clarity of risk/benefit: risk/benefit clear
Methodological strength of supporting evidence: no randomized controlled trials, but randomized controlled trial results can be unequivocally extrapolated; or, overwhelming evidence from observational studies
Implications: strong recommendation; can apply to most patients in most circumstances

1C

Clarity of risk/benefit: risk/benefit clear
Methodological strength of supporting evidence: observation studies
Implications: intermediate-strength recommendation; may change when stronger evidence available

2A

Clarity of risk/benefit: risk/benefit unclear
Methodological strength of supporting evidence: randomized controlled trials without important limitations
Implications: intermediate strength recommendation; best action may differ, depending on circumstances or patients' societal values

2B

Clarity of risk/benefit: risk/benefit unclear
Methodological strength of supporting evidence: randomized controlled trials with important limitations (inconsistent results, methodologic flaws*)
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2C

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Implications: very weak recommendation; other alternatives may be equally reasonable

* Such situations include randomized controlled trials with lack of blinding, and subjective outcomes, in which the risk of bias in measurement of outcomes is high; and randomized controlled trials with large loss to follow-up.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified for each recommendation (refer to "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate treatment with intravenous thrombolysis in patients with acute myocardial infarction may achieve a higher rate of early infarct-artery patency and a lower mortality rate, as well as help manage costs and the risks for potential adverse events, such as major bleeding.

POTENTIAL HARMS

- The main complication of fibrinolytic therapy is bleeding, with the most severe bleeding complication being intracranial hemorrhage, which usually occurs in the first 24 hours after starting therapy.
- There is an excess stroke risk associated with fibrinolytic therapy, largely attributable to the excess risk of intracranial hemorrhage that occurs in the first day after such treatment.

Subgroups Most Likely to be Harmed:

- Several patient characteristics are associated with a higher risk of intracranial bleeding. Table 7 in the original guideline document summarizes predictors of intracranial hemorrhage after fibrinolysis for acute myocardial infarction, the highest predictor being advanced age.
- Certain patient characteristics, such as age, Killip class, and infarct location are associated with much higher 30-day mortality.

CONTRAINDICATIONS

CONTRAINDICATIONS

Intravenous fibrinolytic therapy is contraindicated in patients with prior intracranial hemorrhage, any stroke within the previous year, or active bleeding.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Interpreting the Recommendations

The authors of these guidelines offer recommendations that should not be construed as dictates by the readers, including clinicians, third-party payers, institutional review committees, and courts. In general, anything other than a 1A recommendation indicates that the chapter authors acknowledge that other interpretations of the evidence and other clinical policies may be reasonable and appropriate. Even grade 1A recommendations will not apply to all circumstances and all patients. For instance, the guideline developers have been conservative in their considerations of cost, and have seldom downgraded recommendations from 1 to 2 on the basis of expense. As a result, in jurisdictions in which resource constraints are severe, alternative allocations may serve the health of the public far more than some of the interventions that the guideline developers designate grade 1A. This will likely be true for all less-industrialized countries. However, a weak recommendation (2C) that reduces resource consumption may be more strongly indicated in less-industrialized countries.

Similarly, following grade 1A recommendations will at times not serve the best interests of patients with atypical values or preferences. For instance, consider patients who find anticoagulant therapy extremely aversive, either because it interferes with their lifestyle (prevents participation in contact sports, for instance) or because of the need for monitoring. For such patients, clinicians may reasonably conclude that following some grade 1A recommendations for anticoagulation will be a mistake. The same may be true for patients with particular comorbidities (such as a recent GI bleed or a balance disorder with repeated falls) or other special circumstances (such as very advanced age).

The guideline developers trust that these observations convey their acknowledgment that no guidelines or recommendations can take into account the often compelling idiosyncrasies of individual clinical circumstances. No clinician and no one charged with evaluating the actions of a clinician should attempt to apply their recommendations in a rote or blanket fashion.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Ohman EM, Harrington RA, Cannon CP, Agnelli G, Cairns JA, Kennedy JW. Intravenous thrombolysis in acute myocardial infarction. Chest 2001 Jan;119(1 Suppl):253S-277S. [188 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001 Jan

GUIDELINE DEVELOPER(S)

American College of Chest Physicians - Medical Specialty Society

SOURCE(S) OF FUNDING

Funding was supplied by DuPont Pharmaceuticals.

GUIDELINE COMMITTEE

American College of Chest Physicians Consensus Panel on Antithrombotic Therapy

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: E. Magnus Ohman, MD, FCCP; Robert A. Harrington, MD; Christopher P. Cannon, MD; Giancarlo Agnelli, MD; John A. Cairns, MD and J.Ward Kennedy, MD.

Committee Co-Chairs: James E. Dalen, MD, MPH, FCCP; Jack Hirsh, MD, FCCP.

Participants: Giancarlo Agnelli, MD; Gregory W. Albers, MD; Joseph S. Alpert, MD, FCCP; Pierre Amarenco, MD; Sonia S. Anand, MD; David Anderson, MD; Frederick A. Anderson, PhD; Maureen Andrew, MD; Jack E. Ansell, MD; Peter B. Berger, MD; Edward Bovill, MD; Heiner Bucher, MD, MPH; Henry I. Bussey, PharmD; Christopher P. Cannon, MD; John Cairns, MD; G. Patrick Clagett, MD; Clifford W. Colwell, Jr., MD; Barry S. Coller, MD; Deborah J. Cook, MD, MSc, FCCP; Mark

Crowther, MD; Denise Hartnett Daudelin, RN, MPH; Daniel Deykin, MD; J. Donald Easton, MD; Mark H. Eckman, MD; Michael Ezekowitz, MD; Garrett FitzGerald, MD; Valentin Fuster, MD; William Geerts, MD, FCCP; Michael Gent, DSc; Jeffrey S. Ginsberg, MD, FCCP; Steve Goldman, MD; Christopher Granger, MD; Ian A. Greer, MD; Gordon H. Guyatt, MD; Jonathan L. Halperin, MD; Robert A. Harrington, MD; John Heit, MD; Russell D. Hull, MBBS, FCCP; Thomas M. Hyers, MD, FCCP; Mark R. Jackson, MD; Alan K. Jacobson, MD; Roman Jaeschke, MD, MSc, Clive Kearon, MB, PhD, FCCP; J. Ward Kennedy, MD; Seth Landefeld, MD; Mark N. Levine, MD; Herbert J. Levine, MD; H Daniel Lewis, Jr., MD; A. Michael Lincoff, MD; David Matchar, MD; Kevin M. McIntyre, MD, JD; Thomas W. Meade, DM, Alan D. Michelson, MD; Paul Monagle, MBBS; Timothy A. Morris, MD; E. Magnus Ohman, MD, FCCP; Guy Paiement, MD; Carlo Patrono, MD; Stephen G. Pauker, MD; Palle Petersen, MD, DMSc; Graham Frederick Pineo, MD Leon Poller, DSc, MD; Jeffrey J. Popma, MD; Robert Raschke, MD, MS; Gary Raskob, PhD; Joshua Riff; Gerald Roth, MD; Ralph L. Sacco, MD; Eduardo Salazar, MD; Deeb N. Salem, MD, FCCP; Michel M. Samama, MD; Holger J. Schunemann, MD, MSc; Stephen G. Shaughnessy, PhD; Daniel Singer, MD; Paul D. Stein, MD, FCCP; Victor F. Tapson, MD, FCCP; Philip Teal, MD; Pierre Theroux, MD; Alexander G. G. Turpie, MD; Ted Warkentin, MD; John G. Weg, MD, FCCP; Jeffrey Weitz, MD; and H. Brownell Wheeler, MD.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

GUIDELINE AVAILABILITY

Electronic copies of the updated guideline: Available from the Chest - The Cardiopulmonary and Critical Care Journal Web site.

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Sixth ACCP Consensus Conference on Antithrombotic Therapy (2001): quick reference guide for clinicians. Northbrook, IL: ACCP, 2001.

Electronic copies: Available in from the American College of Chest Physicians Web site. (Downloadable files intended for use with Palm OS compatible devices are available.)

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348, or by calling 1 (800) 343-2227.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on July 30, 2001. The information was verified by the guideline developer on October 17, 2001.

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